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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/027,654	02/23/98	HORTON J	28911/34561

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EXAMINER	
GABEL,G	
ART UNIT	**PAPER NUMBER**
1641	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/027,654	Applicant(s) Horton
	Examiner Gailene R. Gabel	Group Art Unit 1641

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (I) is indefinite and unclear in reciting "to provide a cell lysis fluid" because it does not clearly specify that the lysis reagent lyzed the cells in the sample nor does it clearly define the status of the cells in the sample, i.e. whether or not the cells are lysed in which case the

resultant "fluid" is better referred to as --a lysed cellular sample or mixture--. Furthermore, as claimed, the "cell lysis reagent' and "cell lysis fluid" appear interchangeable. See also steps (ii) and (iii) and claim 11.

Claim 1 (ii) is further confusing in reciting "mixing the cell lysis fluid with reagents" because it does not clearly specify what is encompassed by the term "reagents". Furthermore, it is unclear as to whether there is a relationship between the "reagents" in (ii) and the "cell lysis reagent" in (I).

Claim 1 (ii) is redundant and confusing in reciting "for performing a specific binding assay for the analyte" since it has been established (prior to this statement) in the limitation that the specific binding partner binds to the analyte to perform a specific binding assay. (It is suggested but not required that the language be --to perform a specific binding assay to form a binding reaction mixture-- for clarity and antecedent support for "the binding reaction mixture" in claim 4.)

It is unclear what the relationship is between "the sequestrant" in (iii) and "reagents" in (ii), i.e. is it applicant's intent to refer to two separate elements.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 1 fails to recite elements and method steps to define a detection system which is critical to the claimed invention.

Claims 2-13 have improper antecedent basis problems by reciting "a Method as claimed in claim...". Change to --The method as claimed in claim...-- for proper antecedent basis.

Claim 4 lacks antecedent support in reciting "the binding reaction mixture". (Note suggested language in claim 1 (ii).

Claim 6 is indefinite in reciting "multiple assays" because it does not clearly define what is encompassed by the "multiple assays", i.e. different separate assays as claimed, same reagents used, same specific binding partners, etc. as in claims 8 and 9.

Claim 6 is unclear, confusing, and recites inconsistent language in relation to claims 5 and 7 by reciting "in wells of a multiwell plate" because it appears that the (individual) "wells" are being used synonymously with "vessel".

Claim 7 has improper antecedent basis by reciting "in a vessel". Change to --in the vessel-- for proper antecedent basis.

Claim 7 recites non-idiomatic expression by reciting "that vessel", first and second occurrence. It is suggested but not required to use --said vessel-- or --the vessel--.

Claim 13 is indefinite in the usage of parenthetical symbols since it is unclear as to whether the notation incorporated therein is a part of the limitation in the claim. Claim 13 is unclear and confusing in reciting "concentration is measured of an analyte". Furthermore, claim 13 recites improper Markush language by reciting "an analyte selected from". It is suggested but not required that the following language or equivalent thereof be used to assist the applicant to clarify the claim: --The method as claimed in claim 1, wherein the intracellular or both

intracellular and extracellular concentration of the analyte is measured and the analyte is selected form the group consisting of adenosine-3',5'-cyclic monophosphate, interleukin-6, and prostaglandin E_2 .--

Claim 14 which claims a kit to perform the method as claimed in claim 1 is inconsistent and indefinite for reciting limitations not presented in the method. It is unclear how the claimed method can be practiced using the kit as claimed since claim 14 recites "a tracer" and "a separation means for separating bound tracer from unbound tracer", but the use thereof are not specifically defined in the previously claimed method. Accordingly, claim 1 omits essential steps and fails to recite limitations, i.e. structural and functional elements and steps that are critical to the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-4, 8-11, and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986).

Cook (1) teach that scintillation proximity assay is an established high-throughput screening technology that allows the design of high-flux assays for a variety of biochemical and

cellular targets which requires no separation and relies entirely on "mix and measure" format (see Abstract). Scintillation proximity assay (SPA) which is homogeneous in nature has been applied to various binding interactions which includes cellular adhesion molecule binding, protein-peptide interactions, and cellular biochemistry assays (see page 2, column 2, first paragraph and page 4, column 2). In SPA, the analyte is immobilized to a small scintillant-containing microsphere and a radioisotopically labeled molecule binds to the microsphere, and the radioisotope is brought into close proximity to the scintillant and effective energy transfer from the particle will take place (see page 3, column 1). The SPA microspheres therefore replace the traditional separation steps employed in radioimmunoassay (see Figures 1 and 2). Cook teach that the technology has been used with a broad spectrum of applications including mass measurements in cellular function screening for analytes such as prostaglandins, interleukins, and adenosine-3',5'- cyclic monophosphate (cyclic AMP). Box 1 in page 4 illustrates examples of radioimmunoassay developed using SPA and box 2 in page illustrates examples of receptor-ligand binding assays developed using SPA. Cook (1) fails to teach incorporation of a detergent such as dodecyl trimethyl ammonium bromide and a neutralizing agent such as cyclodextrin.

Lundin disclose a method of extracting analyte (intracellular components) from a cellular sample by mixing the sample of cells with a lysis reagent (extractant) to generate a lysed cellular sample (extract solution) and simultaneously contacting the lysed cellular sample with a sequestrant such as cyclodextrin or a derivative thereof, to sequester (neutralize) the lysis reagent

(see Abstract and column 6, lines 38-49). The lysis reagent used conventionally is detergent (see column 2, lines 43-45). Lundin teach that lysis reagents that rapidly open up cell membranes also simultaneously inactivate enzymes that act on intracellular components causing considerable metabolite changes and therefore separation (removal) of the detergent is necessary (see column, lines 32-48 and column 2, lines 43-48). Cyclodextrin sequesters the lysis reagent by forming a complex with it wherein it is possible but not necessary or desirable to remove the complex from the solution (see column 5, lines 33-52 and column 6, lines 55-67). Cyclodextrin id preferably used in excess of the surfactant on a molar basis considering the stoichiometry of inclusion complex that is formed. Lundin disclose that any lysis reagent and any cyclodextrin may be used as long as the inhibition or inactivation of enzymes is avoided for use in assay procedures. The lysis reagent is preferably a surfactant contacted with which is mixed with α, β, or γ cyclodextrin (see column 7, lines 13-37). The cyclodextrin can be added at any step in the assay method after completion of lysis but always before or simultaneously with the addition of specific binding partners (enzymes) involved in the assay (column 7, lines 28-38). Lysis reagents are selected among various surfactants which include dodecyl trimethyl ammonium bromide (Example 1). The analytes extracted from cells may include intracellular metabolites such as ATP and nucleic acids. Lundin further disclose a kit for lysis and assay of analytes, i.e. ATP comprising a lysis reagent, a cyclodextrin, reagent with specific binding partner, i.e. firefly luciferase reagent, and an assay buffer (see column 7, lines 3-13).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine a detergent such as dodecyl trimethyl ammonium bromide to lyse cellular membranes and a sequestrant such as cyclodextrin for simultaneously neutralizing the detergent as taught by Lundin into the scintillation proximity assays of Cook (1) in order to measure concentration of intracellular and extracellular analytes because Lundin specifically disclose extreme difficulty in extracting analytes from cellular samples while maintaining their functional integrity for use in immunological assays and that dodecyl trimethyl ammonium bromide and cyclodextrin are efficient extraction and neutralizing agents, respectively. One of ordinary skill in the art would have been motivated to combine the teaching of Lundin in extraction of cellular components and neutralization of the extractant with the many scintillation proximity assay applications as discussed by Cook (1) because Lundin specifically teach efficient analyte separation of his method and Cook specifically teach advantages of not requiring separation methods such as convenience, ease, economy and safety from potential hazardous or radioactive materials due to minimal handling thereof. One of ordinary skill in the art would have reasonable expectation of success in selecting the amount of sequestrant used in neutralizing the lysis reagent because reagent concentration selection is conventional and well known in the art. Furthermore, appropriate reagent concentration selections are result effective variables which are dependent upon scientific data acquired resulting from experimentation pursuant to optimization, and standardization of procedures.

4. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986), and in further view of Cook (2) (WO 94/26413).

Cook (1) and Lundin have been discussed supra. Cook (1) and Lundin fail to teach use of a multiwell system for use in both culturing cells and assaying cellular analyte.

Cook (2) disclose an apparatus and method for studying cellular processes using scintillation proximity assay. The apparatus comprises a vessel having a base with a scintillant substance and which is adapted for attachment and growth of cells (see Abstract). Cook (2) further disclose a multiwell plate comprising an array of wells held in fixed relationship to one another wherein each well is a vessel (see page 10, first full paragraph). The scintillant substance include aromatic hydrocarbons which emit light used for detection. The method of studying cellular processes includes introducing into the vessel a sample of cells labeled with a radioisotope emitting electrons, and using detection means to observe scintillation caused by radioactive decay so as to study the cellular process (see page 10, second full paragraph). The multiwell plate can take various formats for the purpose of culturing cells using standard cell culture media and growing cells in a sterile environment at 37 °C in a 95 % humidified air and 5% CO_2 incubator as well as studying cellular biochemical processes in living cells (page 14, second and third full paragraphs and page 15, second full paragraph). Cook (2) disclose that the surface of wells or vessels in the microwell plate requires modification in order to be adapted for the attachment and/or growth of cells. Cook (2) disclose that a considerable advantage of the

scintillation proximity assay is that it does not require separation of bound and molecular species from free, thereby minimizing handling of potentially hazardous substances (see page 7, second full paragraph).

It would have been obvious to one of ordinary skill in the art to incorporate that use of a multiwell system with an array of reaction vessels as taught by Cook (2) into the teachings of Cook (1) and Lundin supra because it allows for minimal handling of materials in high-throughput immunoassay testing and and Cook (1) specifically teach the need for rapid, high flux simultaneous homogeneous assays. One of ordinary skill in the art would have been motivated to incorporate derivatized multiwell systems of Cook (2) into the method of Cook (1) and Lundin because of the high capacity yet efficient system achievable in assaying a wide variety of biochemical and cellular analytes for screening and identification.

5. For reasons aforementioned, no claims are allowed.

Remarks

6. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Baendale et al. (Advances in Prostaglandin, Thromboxane, and Leukotriene Research, 1990) teach development of SPA for prostaglandins and related compounds.

Lundin et al. (US 5,705,345) disclose methods and kits for preparing nucleic acids using cyclodextrin.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

G Gabel 9/29/99

Gail Gabel
Patent Examiner
Group 1641

James C. Housel 10/1/99

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER